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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,623	04/30/2001	Sudhir Agrawal	47508.528	2601

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KEOWN & ASSOCIATES
500 WEST CUMMINGS PARK
SUITE 1200
WOBURN, MA 01801

EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 11/19/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/845,623	AGRAWAL ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-24 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-24 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 25, 2003 has been entered.

The Amendment filed August 25, 2003 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 18 and 27 have been amended.

Claims 25-26 have been canceled.

Remarks drawn to rejections of Office Action mailed June 17, 2003 include:

112 2nd paragraph rejections: which have been overcome in part by applicant's amendments and have been withdrawn in part.

103(a) rejection: which has been overcome by applicants amendments and has been withdrawn.

An action on the merits of claims 18-24 and 27 is contained herein below.

The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-24 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing an immune response in a mammal by administering a CpG dinucleotides and an immunomodulatory moiety wherein the immunomodulatory moiety is an abasic nucleoside or a phosphorothioate linkage, does not reasonably provide enablement for the broad genus of compounds set forth in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

Claim 18 is drawn to a method for inducing an immune response in a mammal comprising: administering to the mammal a compound comprising a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is selected from the group consisting of: one or more abasic nucleosides, a 1,3-propanediol linker which may be substituted or unsubstituted, a 3'-3' linkage, and a modified base containing nucleoside, wherein the modified base containing nucleoside is selected from the group consisting of: inosine, 2-amino-purine, nebularine, 7-deaza-guanosine, nitropyrrole, nitroindole, deoxyuridine, 4-thio-deoxyuridine, d-isoguanosine, d-iso-5-methylcytosine, and P-base; and wherein the compound has a greater immunostimulatory effect than it would if it lacked the immunomodulatory moiety. Claim 19 limits the animal to a human, claim 20 limits the route of administration. Claims 21 and 22 provide an amount of active agent to be taken. Claim 23 provides that the compound is taken in combination with a vaccine, and claim 24 additionally adds an adjuvant. Claim 27 limits G of the CpG dinucleotides to guanosine, 7-deazaguanosine, or inosine.

The state of the prior art

CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) are known to induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Pat. Nos. 6,008,200 and 5,856,462. Phosphorothioate CpG containing oligonucleotides are known to be immunostimulatory (Hutcherson et al. US Patent 5,663,153). Liang et al. teach that

phosphorothioate CpG containing oligonucleotides are known to activate human B cells (J. Clin. Invest. 98:1119-1129, 1996). Moldoveanu et al. teach phosphorothioate CpG containing oligonucleotides enhance immune response against influenza virus (Vaccine, 16:1216-124, 1998). Moreover, the various modified nucleosides and linkages are known in the art.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the active agent, being a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is selected from the group consisting of: one or more abasic nucleosides or a phosphorothioate linkage, is indeed effective at inducing an immune response, however the art is silent with regard to the predictability that any of the cited immunomodulatory moieties are effective in combination with a CpG dinucleotide at inducing an immune response.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy of prevention instantly asserted.

The existence of working examples

The working examples set forth in the instant specification are drawn to the following examples:

Example 1: an in vitro test using mouse spleen lymphocytes cultured with oligonucleotides to determine cell proliferation levels.

Example 2: an in vivo test comprising intraperitonealy administering oligonucleotides to mice and determining spleen weights.

It is noted that the only results shown are those in figures 2B and 3B which show that oligonucleotides D7-131-12 and D7-133-13 increase spleen weight of the mice in example 2. Moreover, oligonucleotides D7-131-13 and D7-13-12 both comprise phosphorothioate linked abasic nucleotides 4 and 5 positions up on the 5' end of the CpG dinucleotide.

There has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that a compound comprising a CpG dinucleotide and any of the claimed immunomodulatory moieties indeed has efficacy as instantly asserted.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable a method of inducing an immune response in a mammal comprising administering a compound comprising a CpG dinucleotide and any of the claimed immunomodulatory moieties as instantly asserted. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Enablement for a single compound cannot provide enablement for the breadth of claims sought in arts which are unpredictable. That is, a single embodiment may provide broad enablement in cases involving predictable factors, but more is required in cases involving

unpredictable factors, such as chemical or physiological activity. See ***Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987)*** and ***In re Shokal, 242 F.2d 771, 113 USPQ 283, 285 (CCPA 1957).***

Claims 18-24 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The structure of claim 18 is confusing. Applicants amendment filed 8/25/03 cleared the previous uncertainty, however, the claim is still confusing and is difficult to ascertain that which is being truly claimed. The examiner has interpreted the claim as the following: "a method for inducing an immune response in a mammal comprising: administering to the mammal a compound comprising a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is selected from the group consisting of: one or more abasic nucleosides, a 1,3-propanediol linker which may be substituted or unsubstituted, a 3'-3' linkage, and a modified base containing nucleoside, wherein the modified base containing nucleoside is selected from the group consisting of: inosine, 2-amino-purine, nebularine, 7-deaza-guanosine, nitropyrrole, nitroindole, deoxyuridine, 4-thio-deoxyuridine, d-isoguanosine, d-iso-5-methylcytosine, and P-base; and wherein the compound has a greater immunostimulatory effect than it would if it lacked the immunomodulatory moiety". It is noted that the claim would be more favorably considered if rewritten as set forth supra.

Claim 18 is drawn to a 1,3-propanediol linker which may be "substituted", but there is no identification on how applicant intends to "substitute" the linker in the claims. In the absence of the identity of moieties which are intended to be substituted, thus altering an art recognized chemical core, described structurally or by chemical name, the identity of "substituted" would be difficult to ascertain. In the absence of said moieties, the claims containing the term "substituted" without defining what is to be "substituted" are not described sufficiently to distinctly point out that which applicant intends as their invention. Applicants defining what is intended by "modified" in their amendment to claim 18 obviated the rejection of "modified" as being indefinite.

Claim 18 is indefinite wherein the claim limits the modified base to optionally "P-base". The examiner is unaware of any compound being referred to as P-base in the nucleotide/nucleoside art and is unclear as to what is intended by the recitation of "P-base". Clarity is respectfully requested.

Claim 23 is indefinite wherein it is unclear if the step of administering the adjuvant is an additional step that is to be administered separately, or if the adjuvant is intended to be administered with the CpG/immunomodulatory/vaccine. Clarity is respectfully requested. It is noted that applicants argue that this claim is definite when read in the context of the specification, particularly where page 12 defines the term "in combination with". However, it is noted that in the examination process, it is proper to use the specification to interpret what applicant intends by a word or phrase recited in the claims, but it is **not** proper to read these limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen,* 30 F. 3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994).

Moreover, it is noted that the definition of "in combination with" on page 12 provides guidance as to various routes which are included in the phrase "in combination with", but there is nothing which clearly sets forth a concise and definitive route of delivery, just routes which may include various requirements.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 103

Claims 18-24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Hutcherson et al. (US Patent 5,663,153) (of record), McCluskie et al. (Cutting Edge: CpG DNA is a Potent Enhancer of Systemic and Mucosal Immune Responses Against Hepatitis B Surface Antigen with Intranasal Administration to Mice", J. Immunol., vol. 161, pp. 4463-66, 1998) (newly cited) and Kuramoto et al. ("Oligonucleotide Sequences Required for Natural Killer Cell Activation", Jpn. J. Cancer Res., vol. 83, pp. 1128-31, November 1992) (newly cited).

Claim 18 of the instant application is drawn to a method for inducing an immune response in a mammal comprising: administering to the mammal a compound comprising a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is selected from the group consisting of: one or more abasic nucleosides, a 1,3-propanediol linker which may be substituted or unsubstituted, a 3'-3' linkage, and a modified base containing

nucleoside, wherein the modified base containing nucleoside is selected from the group consisting of: inosine, 2-amino-purine, nebularine, 7-deaza-guanosine, nitropyrrole, nitroindole, deoxyuridine, 4-thio-deoxyuridine, d-isoguanosine, d-iso-5-methylcytosine, and P-base; and wherein the compound has a greater immunostimulatory effect than it would if it lacked the immunomodulatory moiety. It is noted, as set forth supra, applicants are only enabled for a method of inducing an immune response in a mammal by administering a CpG dinucleotide and an immunomodulatory moiety wherein the immunomodulatory moiety is an abasic nucleoside or a phosphorothioate linkage. Claim 19 limits the mammal to a human. Claim 20 limits the administration to parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal and claim 21 limits the attained blood level of the oligonucleotide to be from about 0.01 micromolar to about 10 micromolar and claim 22 limits the dosage to be about 0.1 mg per patient per day to about 200 mg per kg body weight per day. Claims 23 and 24 provide that the compound may additionally be administered in combination with a vaccine and/or an adjuvant. Claim 26 limits the CpG dinucleotide wherein G is guanosine, 7-deazaguanosine, or inosine.

Hutcherson et al. disclose a method of stimulating a local immune response in cells or tissues by administering an oligonucleotide analog having at least one phosphorothioate bond to the cells or tissues wherein the phosphorothioate analogs have shown to stimulate a local immune response (an immunomodulatory moiety) in animals and humans (column 5, lines 25-30). Examples of the oligonucleotide sequences which contain the immunomodulator are SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, disclosed in sequence listing in columns 15-16, all of which contain the CpG dinucleotide sequence. The sequences of Hutcherson et al. induced an immune response (IL-1α) when the immunomodulator was present (P=S moiety included) and

did not when there was no immunomodulator present (P=O moiety included) (column 10, table 1). The composition of Hutcherson et al. is disclosed as being capable of being administered topically (ophthalmically, vaginally, rectally, intranasally), intralesionally, orally, by inhalation, or parenterally (column 8, lines 8-23). The compositions of Hutcherson et al. enhance the humoral response at a dosage of about 3.3 mg per kg body weight per day (column 14, lines 13-15) and concentrations of approximately 1 micromolar are therapeutically effective (column 12, lines 13-15). Further it is noted that Hutcherson et al. disclose that unmethylated CpG dinucleotides induce B-cell activation (column 4, lines 38-40) and that the oligonucleotides may have altered sugar moieties and altered base units (column 6, line 63 – column 7 line 19). It is noted that Hutcherson et al. do not specifically disclose the modified bases or sugars to be used with their CpG sequence, such as claimed in the instant as an abasic nucleoside, but they do indeed contemplate these modifications to increase the immune response. Additionally, Hutcherson et al. do not teach to add an additional adjuvant to the composition.

McCluskie et al. teach to add an adjuvant such as cholera toxin to a CpG composition wherein the adjuvant (cholera toxin) and CpG act synergistically, giving stronger immunostimulatory responses than those observed with ten times more of either adjuvant alone (abstract). What is not taught by McCluskie et al. is to include an additional immunomodulatory moiety, such as an abasic nucleoside, into the oligonucleotide.

Kuramoto et al. teach of various CpG containing oligonucleotides which show immunological activity wherein the active oligonucleotide lost it's activity when an exchange or a deletion of bases within the 6-mer occurred, but when an exchange or deletion of a base outside the 6-mer showed no negative effects (page 1128, 1 paragraph). Thus, Kuramoto et al. teach to

use abasic nucleosides (a deletion of a base outside the 6-mer) in combination with CpG nucleotides to enhancing immunological activity.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the CpG oligonucleotide composition of Hutcherson et al. with the teachings of Kuramoto et al. and McCluskie et al. before them, as both Kuramoto et al. and McCluskie et al. intend to enhance the immunological activity of the art known CpG dinucleotide sequence. Moreover, Hutcherson et al. do indeed contemplate the use of these modified analogs. One would be motivated to use these various analogs because Hutcherson et al. teach that various modifications may be made to increase the immune stimulation by enhancing uptake, stability, affinity, or other features of the oligonucleotide (column 7, lines 5-10).

Moreover, it is noted that applicant's results and data shown in figures 2B and 3B do not clearly show that the results of the increased immunological activity is due to the additional immunological agent, but could be from the phosphorothioate bonds included in the oligonucleotides. It is noted, that one of ordinary skill in the art would indeed expect that CpG-oligonucleotides with a phosphorothioate bond would indeed have increased immunostimulatory properties, as Hutcherson et al. teach immune stimulation by phosphorothioate CpG oligonucleotides.

JAMES O. WILSON
PRIMARY EXAMINER
Art Unit 1623

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh III
November 11, 2003